

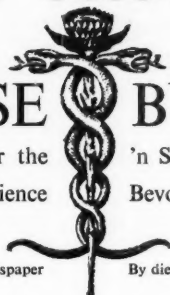
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# MEDICAL PROCEEDINGS

## MEDIESE BYDRAES

A South African Journal for the  
Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die  
Bevordering van die Geneeskunde



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Johannesburg  
5 September 1959

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1. Brown, E.B., Jr. *The Management of Iron Deficiency Anemia*, GP, 2:87 (Feb. 1958).

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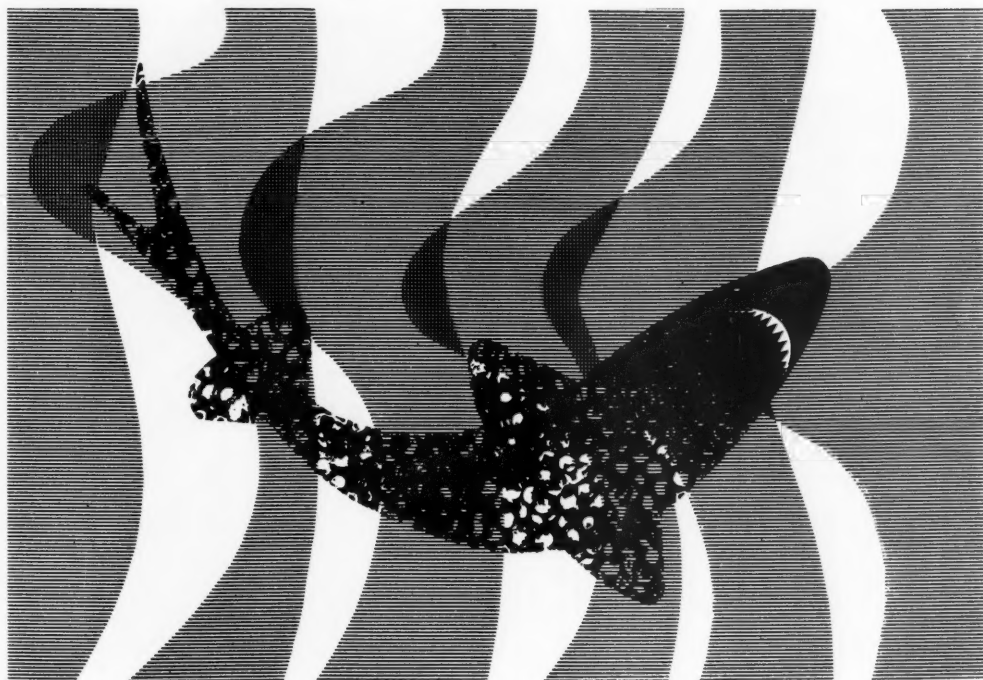
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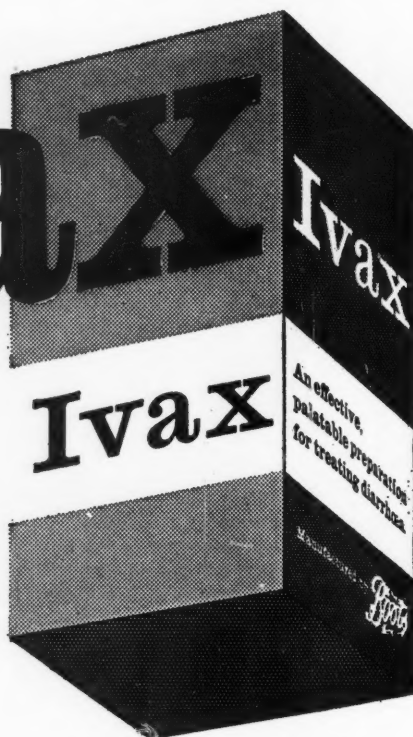
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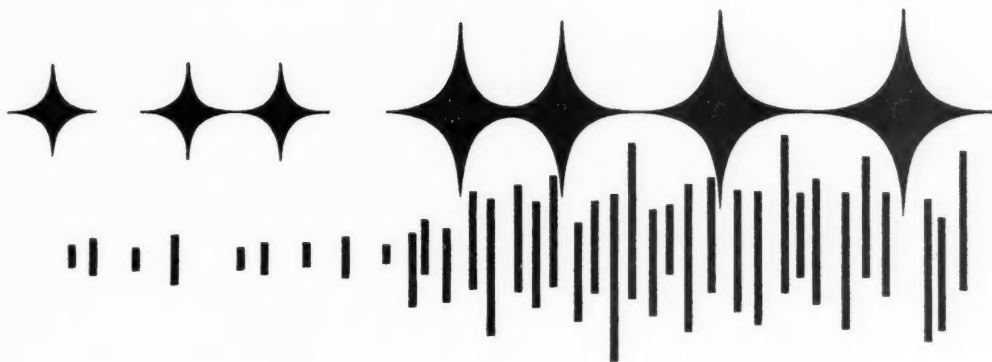
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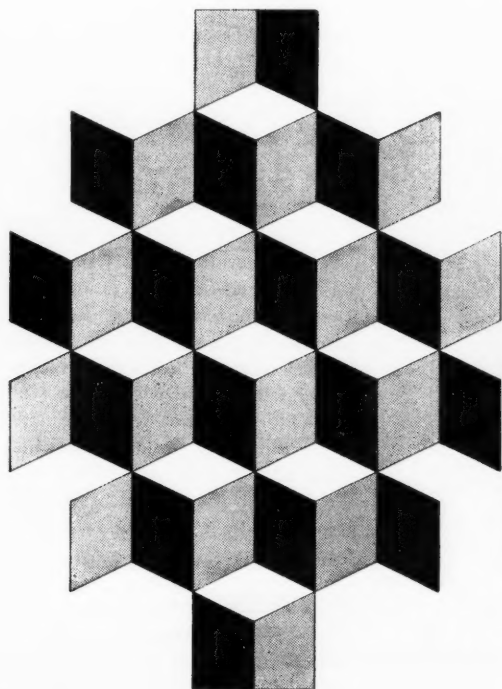
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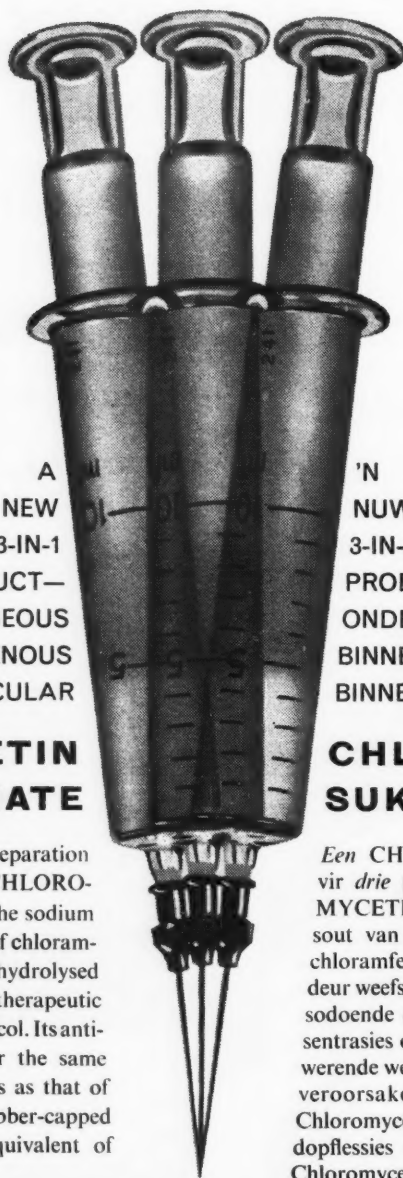
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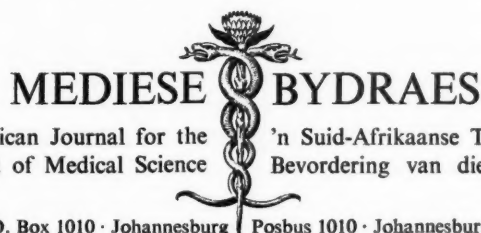
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# MEDICAL PROCEEDINGS



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Vol. 5

5 September 1959

No. 18

## EDITORIAL · REDAKSIONEEL

### THE FIRST CHAIR IN ANAESTHETICS IN SOUTH AFRICA

DR. O. V. S. KOK APPOINTED

Dr. O. V. S. Kok (who has been Head of the Department of Anaesthetics for the past 18 months) has been appointed to the Chair of Anaesthetics at the University of Pretoria, with effect from January 1960.

This is the first professional appointment in South Africa to a Chair of Anaesthetics and is a fitting (if not overdue) recognition of the important role which modern anaesthesia has come to play in the practice of medicine.

Dr. Kok was born at Frankfort, O.F.S., where he matriculated. He took the M.B., Ch.B. degrees at the University of Cape Town in 1934. As an undergraduate he was Head Student of Men's Residence and Vice-President of the Students' Representative Council. He was in general practice until he received the Billroth Scholar-

### DIE EERSTE LEERSTOEL IN ANESTESIOLOGIE IN SUID-AFRIKA

DR. O. V. S. KOK BENOEM

Dr. O. V. S. Kok is met ingang Januarie 1960 tot professor in Anesthesiologie aan die Universiteit Pretoria benoem. Dr. Kok sal dan nie alleen professor wees nie maar ook hoof van die Departement Anesthesiologie. Hy het die laasgenoemde pos reeds die afgelope anderhalf-jaar beklee.

Dit is die eerste professorale benoeming in Suid-Afrika in 'n leerstoel van Anesthesiologie en 'n passende, indien nie late erkenning van die belangrike rol wat die moderne anesthesie reeds in die mediese praktyk inneem het.

Dr. Kok is op Frankfort in die Vrystaat gebore en het in sy geboortedorp gematrikuleer. Hy het in 1934 aan die Universiteit Kaapstad die grade M.B., Ch.B., behaal. Voordat hy gegradueer het, was hy hoofstudent aan die manstehuis en ondervoorsitter van die Studente Verteen-



Dr. O. V. S. Kok

ship, which gave him an opportunity to pursue postgraduate studies in gynaecology and paediatrics in Berlin. Thereafter he went to the University of Liverpool, where he obtained the Diploma in Tropical Medicine. He also continued with further postgraduate work in paediatrics at the Postgraduate Medical School, Hammersmith, whereafter he returned to South Africa to resume his general practice in Johannesburg and the West Rand.

After the war Dr. Kok returned to London to specialize in anaesthetics. Towards the end of 1945 he received the Diplomas in Anaesthetics of the Royal College of Physicians and Surgeons of England and of Ireland. After another year in general practice, Dr. Kok established himself as a specialist anaesthetist in Pretoria and was at that time appointed Lecturer in Anaesthetics at the University of Pretoria. In 1951 he assumed full-time duties as Senior Lecturer in the Division of Anaesthetics of the Department of Surgery of the University of Pretoria, and Chief Anaesthetist to the Pretoria General Hospital. In 1954 he was made a Fellow of the Faculty of Anaesthetists of the Royal College of Surgeons of England, a very meritorious and distinguished honour. He was made Head of the Department of Anaesthetics in 1958, being appointed to the Chair after only 18 months as the Departmental Head.

Dr. Kok is well known for his active interest in research in connexion with the problems of anaesthesia. He has published a variety of papers including studies of such important topics as status lymphaticus, steroid anaesthesia (Viadril), the causes of death associated with anaesthesia, cardiac arrest, etc. He is the Honorary Director of the CSIR project investigating the causes of death associated with anaesthesia and surgery and is at present actively engaged in supervising the investigations of a full-time Senior Bursar working on these problems.

Dr. Kok's interests extend widely beyond the field of his speciality. He is President-Elect of the South African Society of Anaesthetists, a Member of the Executive Committee of the Anaesthetists Section of the South African College of Physicians, Surgeons and Gynaecologists and he is the Honorary Secretary of the Northern Transvaal Branch of the Medical Association of South Africa.

At the beginning of this year, as Associate Editor, he was responsible (jointly with Prof. H. W. Snyman and Dr. W. J. Pepler) for establishing *Geneeskunde*, the first medical journal to be published wholly in Afrikaans—an historic event.

woordigende Raad. Hy het 'n algemene praktyk beoefen totdat hy die Billroth-beurs ontvang het wat hom die geleentheid gegee het om sy nagraadse studies in ginekologie en pediatrie in Berlyn voort te sit. Daarna is hy na die Universiteit Liverpool waar hy die Diploma in Tropiese Siektes behaal het. Hy het ook met verdere nagraadse werk in die pediatrie aan die *Postgraduate Medical School*, Hammersmith, voortgegaan en daarna teruggekeer na Suid-Afrika om sy algemene praktyk in Johannesburg en aan die Wes-Rand te hervat.

Na die oorlog het dr. Kok na Londen teruggekeer om in die anesthesiologie te spesialiseer. Teen die einde van 1945 het hy die Diplomas in Anesthesiologie van die *Royal College of Physicians and Surgeons* van Engeland en van Ierland behaal. Na nog 'n jaar van algemene praktyk het dr. Kok homself as narkotiseur-spesialiteit in Pretoria gevestig. Op daardie tydstop is hy tot lektor in Anesthesiologie aan die Universiteit Pretoria benoem. In 1951 het hy voltydse pligte aanvaar as Senior Lektor in die afdeling Anesthesiologie van die Departement Chirurgie van dieselfde Universiteit en as hoof-narkotiseur van die Algemene Hospitaal, Pretoria. In 1954 het hy 'n *Fellow* geword van die *Faculty of Anaesthetists* van die *Royal College of Surgeons* in Engeland wat 'n uiters verdienstelike en voortrefflike onderskeiding is. In 1958 is hy bevorder tot hoof van die Departement Anesthesiologie. Hy is dus tot die leerstoel benoem nadat hy slegs 18 maande Hoof van die Departement was.

Dr. Kok is bekend vanweë sy daadwerklike belangstelling in navorsing in verband met die probleme van anestesie. Hy het reeds verskillende verhandelings gepubliseer, waarby ingesluit is studies van sulke onderwerpe soos status limfatikus, steroïede anestesie (Viadril) die oorsake van die dood wat in verband staan met anestesie, hartstilstand, ens. Hy is ere-direkteur van die WNNR se onderneming vir ondersoek na dood wat in verband staan met anestesie en chirurgie en hou op die oomblik ook aktief toesig oor die ondersoek van 'n voltydse senior beurshouer wat aan dié probleem werk.

Dr. Kok se belangstelling strek veel verder as net die gebied wat sy spesialiteit is. Hy is die pas-verkose president van die Suid-Afrikaanse Vereniging van Narkotiseurs, 'n lid van die Uitvoerende Komitee van die afdeling Narkotiseurs van die Suid-Afrikaanse Kollege van Interniste, Chirurgie en Ginekoloë en hy is ere-sekretaris van die Noord-Transvaalse tak van die Suid-Afrikaanse Mediese Vereniging.

Aan die begin van die jaar was hy in die hoedanigheid van mederedakteur, saam met prof. H. W.

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Dr. Kok's considerable experience in many diverse branches of medicine fits him pre-eminently for his new post, to which he will bring not only enthusiasm, but also the wisdom gathered in the course of many years of practice; and it may well be that the task of the University of Pretoria was simplified in having so distinguished a practitioner as Dr. Kok available for the Professorial Chair.

The lead taken by the Pretoria Medical School in this regard has emphasized the great need for additional Chairs at the other Medical Schools in South Africa. It is only in this way that the teaching of anaesthetics can attain that status which the subject warrants and needs if we are to maintain high standards of instruction (including the requirements of undergraduates) and, equally important, adequate facilities for more intensive concentration on the many research problems which await investigation in the field of pure research, as well as timely participation in the rapid developments taking place in modern surgery.

It is gratifying that the University of Pretoria has recognized the academic importance of this field of teaching and practice and it is to be hoped that the sister universities in the rest of the country will not lag behind in emulating this example.

Snyman en dr. W. J. Pepler, verantwoordelik vir dié tot standkoming van *Geneeskunde* die eerste mediese tydskrif wat geheel en al in Afrikaans gepubliseer word. Dit is 'n geskiedkundige gebeurtenis.

Dr. Kok se rype ervaring in baie uiteenlopende vertakkinge van die geneeskunde stel hom by uitnemendheid in staat om sy nuwe betrekking te behartig—'n taak wat hy nie alleen met geesdrif sal verrig nie maar ook met die wysheid wat hy gedurende baie jare in die praktyk opgedoen het; en dit kan wel wees dat die Universiteit Pretoria se taak vereenvoudig was deurdat so 'n voortreflike praktisyn as dr. Kok vir die professorale stoel beskikbaar was.

Die voortou wat die Pretoriase Mediese Skool in hierdie verband geneem het, beklemtoon die groot behoefte wat daar by ander mediese skole in Suid-Afrika aan bykomstige leerstoel bestaan. Alleen op hierdie wyse kan die onderrig in anesthesiologie die status verkry wat die onderwerp regverdig en vereis indien ons hoë standaarde van onderrig (met insluiting van die vereistes van studente wat nog nie hulle grade het nie) wil handhaaf, en wat net so belangrik is, voldoende fasiliteite wil voorsien om intensiewer aandag te skenk aan die talle navorsingsvraagstukke wat nog nie aangeraak is nie en as ons tred wil hou met die snelle ontwikkeling wat in die moderne snykunde plaasvind.

Dit stem tot dankbaarheid dat die Universiteit Pretoria die akademiese belangrikheid van hierdie gebied van onderrig en praktyk erken het en 'n mens wil vertrou dat die suster-universiteite in die res van die land eerlank ook hierdie voorbeeld sal volg.

## PORTAL HYPERTENSION\*

### MODERN CONCEPTS OF ITS PATHO-PHYSIOLOGY AND ITS SURGICAL APPROACH

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The subject of my talk this afternoon is portal hypertension with special reference to those pathophysiological aspects of it which are primarily of interest to the surgeon. I shall restrict my remarks only to the intrahepatic factors. The extra-hepatic lesions will be mentioned cursorily and then only for differentiation.

As the surgeon's interest in portal hypertension resulting from cirrhosis of the liver is confined to the oesophageal varices and the resulting haemorrhage, it would be as well to ask at once how formidable the problem of liver cirrhosis is to-day; how frequent the incidence of haemorrhage is in liver cirrhosis;

what the chances of survival are in a patient who has such a haemorrhage when treated by medical means alone and to what extent these can be modified by surgical methods.

In a *Statistical Bulletin*<sup>1</sup> issued by the Metropolitan Life Insurance Company of New York in 1957, it was revealed that cirrhosis of the liver has become the fourth most frequent cause of death in persons between 45 and 60 years of age in the United States, being exceeded only by heart disease, cancer and cerebral haemorrhage. In South Africa Becker stated in 1944 that hepatic cirrhosis was the cause of death in one out of every 26 European, and one out of every 16 non-European autopsies held in the Johannesburg Hospital. It is therefore one of the major problems in

\* An address delivered before the Department of Surgery, Harveian Lecture Theatre, Johannesburg.



medicine to-day. How major a problem it was among the primitive people and among the several civilizations of antiquity can only be conjectured. Certainly, the Babylonians three thousand years ago practised hepatoscopy, or the reading of omens in the signs noted on the liver of sacrificial animals, as a method of divining the future. Terra cotta models of these livers have been found, the surfaces of which have been divided into squares and studded with prophetic inscriptions.<sup>2</sup> In this modern age we, who are also attempting to divine the future of the cirrhotic subject, are obliged to resort to the facts which we can obtain and those lessons which we can learn from the recorded experiences of the clinical observer and the pathologist.

Thus we are able to say that the incidence of haemorrhage in cirrhosis is given as 20% by Evans and Gray in 1938, 29% by Cates in 1956, and 38% by Chase *et al.* in 1957;<sup>3</sup> and as 27% by Ratnoff and Patek in 1942, and 33% by Ratnoff and Patek again in 1955. When haemorrhage does occur, it is terminal in 40% of cases, and a further 30% die within a year. Welch *et al.*,<sup>4</sup> who studied 50 patients with massive haemorrhage from varices and portal hypertension found that 33 died in hospital (66%) and, of the 17 survivors, 7 died within a year, making a total mortality of 80% within a year. Child and Donovan<sup>5</sup> stated that 40–60% of patients with cirrhosis are dead within a month of their first haemorrhage. Very recently, Baker, Smith and Lieberman<sup>16</sup> published a study of 115 cirrhotic patients in whom oesophageal varices had been diagnosed before bleeding had taken place and whom they followed for varying periods from 1–6 years (average 3.3 years); 28.6% had bled, 17.3% had died of exsanguination, 26% had died of hepatic failure, 20% had succumbed to unrelated causes, 9.5% died of exsanguination during the first episode of bleeding, and about 90% of the deaths from liver disease occurred within 2 years after varices were diagnosed.

To what extent this terrible toll of life can be ameliorated by surgical intervention was indicated by Linton<sup>6</sup> who stated that after 13 years of experience with the type of surgery which will protect the liver from repeated insults due to recurring oesophageal haemorrhages, there can be no question that life has been prolonged in many instances and that the majority of patients have been rehabilitated, with a marked reduction in morbidity.

Apart from this aspect of haemorrhage, it should of course be remembered that the func-

tional problem of cirrhosis is characterized by three other cardinal features,<sup>1</sup> viz.: reduced hepatic function, ascites, and a tendency to progression of the liver disease.

It is worth while at this point to consider briefly the pathological changes in the liver which create eventually those circumstances which make a surgeon's intervention not only desirable but also very necessary, and then to discuss some of the pathophysiological aspects.

The portal vein branches in a cirrhotic liver show deformities and irregular arrangements, but the arteries appear normal. The hepatic vein tributaries, however, not being so well protected by surrounding connective tissue, hepatic arteries and bile ducts as the portal vein branches are, are compressed where they cross between regenerative nodules of liver cells and are distorted by fibrosis. This post-sinusoidal compression interferes with the drainage of blood from the liver and is thus one of the main causes of portal hypertension in cirrhosis. Since smaller nodules compress veins more effectively than larger ones, they are associated with a greater tendency to portal hypertension. The contribution of the hepatic arteries to the nodules is greater than to the normal parenchyma and it is therefore not surprising to find that in a similar way arterial branches contribute more to the vasculature of primary or secondary hepatic carcinoma. In many places para-sinusoidal communications between branches of the portal and hepatic veins are noted which shunt blood from the former to the latter, by-passing the parenchyma. The functional efficiency of these porto-hepatic anastomoses is disclosed in many interesting ways, e.g. metastatic carcinoma is exceedingly rare in a cirrhotic liver but extremely common in a normal liver. Lieber<sup>7</sup> showed that whereas 28.6% of all carcinomas metastasized to a normal liver, only 0.12% of all carcinomas metastasized to the cirrhotic liver. Furthermore, the tendency for enterobacteria to produce bacteraemia in the patient with liver disease is well known.

The para-sinusoidal anastomoses between portal vein and hepatic arterial branches also are present in cirrhotic livers, and through these anastomoses arterial pressure is brought to bear upon the portal venous system to contribute to the portal hypertension.

The regenerative nodules, by producing post-sinusoidal obstruction of the hepatic vein tributaries, are responsible for most of the portal hypertension in cirrhosis. The perisinusoidal communications between portal vein and hepatic arteries represents the second cause



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of portal hypertension. The third potential cause (distortion of portal vein branches by fibrosis) seems to be of less significance in the cirrhotic process.

Ascites in cirrhosis is induced by post-sinusoidal obstruction of hepatic blood flow as well as by hepatocellular damage. The interference with blood drainage not only raises the portal pressure but also, because of its post-sinusoidal location, increases the formation of hepatic lymph, which escapes through the hepatic capsule into the peritoneal cavity.

Portal hypertension<sup>17</sup> develops as a result of the increased resistance to the normal out-flow of blood from the portal bed into the systemic venous system:

(1) Because of an intrahepatic block, due to the interlobular scarring and the regeneration of liver lobules secondary to portal cirrhosis; or

(2) Because of an extrahepatic block due to an obstruction of the portal vein itself, usually the result of venous thrombosis or, in a rare case, congenital atresia.

The pressure in the portal vein is not extremely great in these conditions, since it is usually found between 25–45 mm. Hg. or 30–60 cm. H<sub>2</sub>O. It is believed that in addition to the portal hypertension there also exists portal hypervolaemia, another important factor that plays a vital role in the pathological physiology of portal bed block. The general pathological picture of portal bed block usually develops over a period of years and may be associated directly with the primary cause of the block. This is especially true in cases of cirrhosis of the liver. It is important to remember from the therapeutic view point that the correction of the bleeding tendency from oesophageal varices by reducing the state of portal hypertension by some type of venovenous anastomosis between the portal and the systemic venous systems has little if any effect on improving the condition of the diseased liver other than protecting it from the ravages of repeated blood loss from severe haemorrhage. Therefore the treatment of the cirrhotic liver should be entirely separate and should be continued indefinitely in most cases.

Sudden occlusion of the portal vein by its interruption in a normal human being results in an extreme degree of portal hypertension, and death usually ensues within a few hours because of haemorrhagic shock resulting from the pooling of the great majority of the circulating blood in the splanchnic area. The portal vein is unique in this regard since almost any large venous channel in the body, except the inferior vena cava proximal to the renal veins, may be interrupted without serious consequences to the individual. This is due

to the paucity and the small size of the collateral venous channels that allow blood to escape from the portal area into the systemic venous system. The obstruction that results from disease, on the other hand, is usually compatible with life at least for varying periods of time, since it is a gradual process in most instances, permitting the venous channels to dilate and so allow the portal blood to by-pass the site of obstruction. As a result the degree of hypertension is not as marked as in acute obstruction of the portal vein, and although it may be 3 or 4 times the normal portal venous pressure, the actual level is not extremely high. Therefore it is believed that too much emphasis has been placed on the term 'hypertension' in these conditions, and not enough on the portal bed hypervolaemia which, it is believed, is greatly increased.

The obstruction to the outflow of the portal venous blood produces definite changes which are not compatible with good health. These include changes in the cellular constituents of the blood, due in part to hyperactivity of the spleen—so-called congestive splenomegaly or hypersplenism. Marked changes may occur also in the function of the liver in the intra-hepatic group, and also late in the course of the disease in long-standing cases of the extra-hepatic type of portal bed block. One of the most significant changes which occurs, however, is vascular in nature, especially since it represents a serious threat to life. Thus, as a result of the portal obstruction to the out-flow of blood from the portal bed, with the resulting state of portal hypertension and hypervolaemia, marked engorgement and enlargement of the venous collateral channels develop, especially of the submucosal veins of the lower portion of the oesophagus. Although ill health may result from the primary liver disease and secondary blood changes, it is of extreme significance that death may occur with cataclysmic suddenness from rupture of these oesophageal varices due to exsanguinating haemorrhage. This is much more likely to occur in patients with cirrhosis of the liver than in those with the extrahepatic type, since patients with normal livers can withstand severe bleeding better than those with diseased livers.

The portal venous system is unique for a number of reasons:

i. It consists of two capillary beds: one in the gastro-intestinal organs, the pancreas and the spleen, and the other in the liver. They are connected by the portal vein and its tribu-

taries which collect the blood from the former and then deliver it to the latter.

ii. The venous pressure in the portal vein and its tributaries is higher than in the systemic veins in this region of the body because the blood must be forced through the second capillary bed—the liver sinusoids. The normal portal pressure has been reported to range between 14 and 22 cm. of saline, according to Bellis, and between 16 cm. and 14 cm. according to Whipple, whereas the normal systemic venous pressure is about zero.

iii. The collateral venous channels between the portal and the systemic venous systems are relatively small in size and few in number, so that sudden occlusion of the portal vein itself results in death from the reduction in the circulating blood volume due to the trapping of large quantities of blood in the splanchnic area.

iv. Unlike most other veins in the body, these blood vessels contain no valves, so that the direction of the blood flow in them may be reversed. This is, in fact, of extreme significance in the consideration of venous shunt surgery, because it makes it possible to by-pass either an intrahepatic or an extrahepatic type of portal bed block.

The blood flow to and through the liver is of interest, since this organ is supplied by both arterial and venous blood, the former by the hepatic artery (said normally to furnish about 25% of the blood supply). The hepatic arterial flow has two functions:

- i. To supply oxygen to the liver cells; and
- ii. To control in part the venous blood flow through the liver.

The latter is accomplished in part due to the fact that the liver is a sponge-like structure. As a result of the high arterial pressure, the organ develops a certain degree of turgidity which exerts a variable degree of pressure on the liver sinusoids, depending on the arterial blood pressure level and, therefore, resistance to the flow of blood through them. At low arterial pressures the portal bed will empty more readily than at higher levels of systemic arterial pressure.

The remaining 75% of blood flowing through the liver is supplied by the portal vein. This blood is relatively hypoxic so that the liver does not depend on it for oxygen. The chief function, on the other hand, is to carry nutrient material from the intestines for storage in the liver, and insulin from the pancreas, and to carry away from it materials such as glycogen that have been stored in the liver cells. In addition, and of extreme importance, toxic materials resulting from the break-

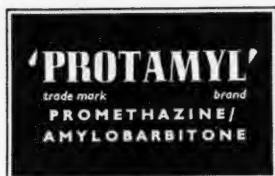
down of proteins in the intestinal tract and which are absorbed by the blood stream, are carried through the liver where they are detoxified before the blood passes on into the general circulation. When all the portal blood is made to by-pass the liver by means of an anastomosis between the portal vein and the inferior vena cava, the detoxifying function of the liver may be impaired seriously with dire consequences, especially in patients with normal livers.

Fortunately, the toxic effects of porto-caval shunts are not so marked in many of the patients with portal hypertension due to an abnormal increase in the arterial blood flow through the hepatic artery seen in this condition. This is thought to be explained by the fact that the blood, although it does not go directly from the intestinal tract to the liver, does reach it in greater quantity per unit of time because of this increased arterial blood flow through it, especially in the cirrhotic liver. Another factor may be that the body has adjusted itself to the effects of the toxic substances as a result of the existing natural vascular shunts which, because they are small, are not effective in reducing the state of portal hypertension but permit a considerable amount of blood with its toxic materials to by-pass the liver, so that the body may develop a certain degree of immunity to them.

As mentioned previously, there is an inter-relationship between the portal venous and arterial blood flow through the normal liver. Elias and Kely showed that the arterial capillaries may join the sinusoids in the para-, the portal, or the intralobular regions, and the blood from them is drained out through the efferent central collecting veins. In 1907, Herrick showed that in the normal liver there is only a slight regurgitation of the hepatic arterial blood into the hepatic portal venous radicals, because there is no abnormal mechanical obstruction to the flow of blood from the liver sinusoids. In portal cirrhosis of the liver, changes take place in this haemodynamic arrangement which, it is believed, play a role in the state of portal hypertension. Herrick showed by perfusion experiments of the liver that at an arterial blood pressure of 130 mm. Hg. in the normal liver some blood flows into the portal vein, and a pressure of 13 to 14 mm. Hg. develops in it, whereas under similar perfusion experiments of livers with portal cirrhosis, the portal pressure rises several times higher to 30–40 mm. Hg. These experiments and others he performed demonstrated that there is a marked regurgitation of arterial



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blood into the intrahepatic portal venous radicals in portal cirrhosis and that there is a much freer communication in this condition between the arterial and the venous channels than in the normal liver.

It is believed that this abnormal capillary type of arterio-venous shunt within the liver in portal cirrhosis is an important factor in producing the state of portal hypertension and hypervolaemia. Additional factors are:

1. The larger volume flow through the hepatic artery observed in the cirrhotic liver as compared with the normal; and

2. The obstruction to the venous outflow through the hepatic veins, the result of fibrosis and the irregular masses of regenerating liver cells.

These abnormal pressure relationships, it is believed, give the only rational reason for the interruption of the hepatic artery as a method of treatment of portal hypertension. It should be noted, however, that since this surgical procedure is so unphysiological from other standpoints, and since so many patients develop liver necrosis from interruption of the hepatic artery, this method of treatment is to be condemned.

The splenomegaly, the abnormalities of the cellular constituents of the blood and the vascular changes in the oesophagogastric-intestinal tract, including the dilatation of the submucosal oesophageal veins to a varicose state, are believed to develop secondary to the state of portal venous hypertension and hypervolaemia. Some of these changes, even though the portal venous pressure may be reduced to a normal level by a portacaval anastomosis, do not revert to normal. Thus the enlarged spleen, especially in long-standing cases, does not reduce to its normal size, nor do the oesophageal varices always disappear. On the other hand, the secondary blood changes often revert to normal.

The normal portal venous pressure, when ascertained in the circumstances of a surgical laparotomy, varies considerably with the depth and the type of anaesthesia and the level of the systolic blood pressure. The normal range is regarded as being between 6–20 cm. of saline, so that pressures above the latter figure indicate the presence of a portal bed block with portal hypertension. In patients with bleeding oesophageal varices secondary to intrahepatic and extrahepatic portal bed block, pressures have been found to be 4–5 times the normal level. In Linton's clinic the highest level encountered has been 54 cm. of saline. The majority lie between 40–50 cm. So far as the blood pressure within the veins of the

portal bed is concerned, it is relatively low when compared with that in the veins of the lower extremity while in the standing position, and yet rupture of the latter with haemorrhage is a relatively rare condition. The course of events that leads to fatal exsanguination from bleeding oesophageal varices would indicate that their rupture results perhaps from trauma or hepatic digestion of the overlying oesophageal mucosa, rather than the increased pressure within them. The relief of bleeding from the oesophageal varices following shunt surgery would indicate that it is not so much the reduction in venous pressure in the portal area as it is the shunting of a large volume of dammed-up blood in the portal area, since the venous pressure after completion of the shunt may still be above the normal range, but bleeding from the oesophageal varices rarely occurs.

It may also be of some practical interest to note at this point that the intravenous administration of 20 units of obstetric Pituitrin diluted to 200 ml. with isotonic saline given over a period of 20 minutes will produce a marked decrease in portal vein pressure, a pronounced delay in circulation time from spleen to liver and from spleen to hepatic vein without a significant change in cardiac output and little change in peripheral arterial resistance. Davis *et al.*<sup>9</sup> states that the temporary or even prolonged lowering of portal pressure in this way would be of benefit in the emergency management of patients with acute haemorrhage from varices.

When Chester Jones *et al.* realized that 65 admissions during 1946–1950 for bleeding oesophageal varices with portal cirrhosis, 32 (49%) died either directly or indirectly from oesophageal haemorrhage whilst attempts were being made to prepare them for surgery, it was decided that exsanguinating oesophageal haemorrhage was to be treated as a surgical emergency and the procedure adopted was as follows:

1. Pass the intragastric balloon: this will stop bleeding in a few minutes.

2. Restore the blood volume quickly by repeated blood transfusions and prepare the operating room.

3. In a matter of a few hours, unless the patient is in impending liver failure, take the patient to the operating room and suture the varices through a trans-thoracic trans-oesophageal exposure. This procedure should be carried out as soon as possible rather than waiting to see if bleeding will recommence when the tube is removed in 24–48 hours, which not infrequently occurs and when it does the patient is usually in a much worse condition to withstand surgery of this magnitude.

In Linton's experience only half of the patients with bleeding varices bled in this

manner, so that it was not always necessary to carry out tamponage or emergency surgery. The decision as to which patients should have their varices sutured was made by selecting only those in whom it was necessary to institute balloon tamponage.

The suturing of the vein was regarded only as the first stage of a 2-stage operative programme. Fortunately it controlled the bleeding in most patients for a period of 6 weeks to 2 months, thereby permitting more thorough preparation of the patient for the larger surgical procedure of constructing some type of portacaval shunt. During the past 7 years, 30 patients were treated by this plan, and 24 (80%) survived the procedure.

Every patient who has bled from oesophageal varices should be considered a candidate for some type of shunt rather than any other procedure or method of therapy, and each patient must be carefully evaluated from the standpoint of liver function before surgery, since selection of the time for shunt surgery is critical, especially in those who are in a generally depleted condition with a failing liver and in whom operation must be delayed until they have been properly prepared.

The evaluation is made on clinical and laboratory grounds only. Liver biopsy has been abandoned. From the clinical point of view, it was found that a palpable liver was associated with a very high incidence of post-operative liver failure, the presence of jaundice would yield poor results, and the presence of spider angiomas was associated with a twofold increase in post-operative liver failure. Also ascites not responding to medical measures was considered to be of serious significance. Thus an ordinary bed-side examination would furnish valuable guides to the operability of the patient.

The following laboratory studies were used routinely in order of importance:

1. Serum albumin.
2. Cephalin flocculation.
3. Prothrombin time.
4. Serum bilirubin level.
5. B.S.P. retention test.

Of these, the serum albumin was the most significant in determining operability, since in 6 patients with a level below 3% there were 5 deaths following shunt surgery from operative and post-operative haemorrhage, a mortality rate of 83%. In 69 patients with level above 3 g. %, there were only 6 operative deaths (9%). Thus the rule is now that the level must be above 3 g. % in all patients undergoing surgery. If it is not, intravenous

administration of human serum albumin is given.

In 36 cases with a cephalin flocculation of +++ to ++++ there were 11 deaths (mortality 21%). In 39 cases with + or ++ there were no deaths.

A prolonged prothrombin time not responding to vitamin K means severe liver disease. A bilirubin level grossly raised requires deferral until jaundice has cleared.

B.S.P. is not a valuable test unless there is 20% or more retention.

The decision whether or not to operate on a patient with a seriously damaged liver does not depend only on the results of one or two of these liver function tests, except when the serum albumin level is below 3 g. %, but also on the over-all condition of the patients.

Linton stated that his group did not select patients for shunt surgery but instead they selected the optimum time for surgery with each patient.

Analyses of the shunt procedures have been published in connexion with earlier phases of the work by Ellis *et al.* (1956)<sup>13</sup> and Ebeling (1956).<sup>14</sup>

I should like to record my indebtedness to Prof. D. J. du Plessis for his interest, and my deep sense of gratitude to Mr. A. Lee McGregor for his encouragement.

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## MEDICINAL NITROFURANS

## A REVIEW

DAVID JACK, B.Sc., F.P.S., A.R.I.C.

*Smith, Kline and French Laboratories, Ltd., London*

In 1944 Dodd and Stillman<sup>1</sup> first showed that nitrofurans possessed marked anti-bacterial activity. Of 25 nitrofurans examined, 24 had highly significant activity against both Gram-positive and Gram-negative organisms. Of these, nitrofurazone (Furacin) was selected for clinical trials and was used with outstanding success for the treatment of war wounds infected with organisms resistant to penicillin and sulphonamides, the major anti-bacterial drugs available at that time.<sup>2</sup> Since then, because of its wide anti-microbial spectrum, nitrofurazone has found new applications, particularly in veterinary medicine. In addition, about 500 new nitrofurans derivatives have been tested and several of these have been introduced into human and veterinary medicine.

## CHEMICAL AND PHYSICAL PROPERTIES OF NITROFURANS

The chemical names and structures for the more important nitrofurans derivatives are given in Table 1. It is apparent that each is formed by condensation of

5-nitro-2-furaldehyde with an organic base, all but one of the latter being substituted hydrazines.

These nitrofurans are yellow crystalline solids. In general, they are rather sparingly soluble in water, forming neutral or slightly acidic solutions, and are also sparingly soluble in most common organic solvents. For laboratory purposes more concentrated solutions may be made in polyethyleneglycols or dimethylformamide. The solids are stable but darken in colour when exposed to light. This is essentially a surface phenomenon and little loss of activity occurs. Nitrofurans are also stable in neutral and acid solutions but darken and decompose in alkali. In this respect they differ from most simple furans which are unstable to acid and relatively stable to alkali.

## ANTI-MICROBIAL SPECTRA OF NITROFURANS

The approximate sensitivities of the more important bacteria to nitrofurans are summarized in Table 2 to illustrate their wide range of activity. A range of inhibiting concentrations indicates that more than one strain was tested. More complete spectra have been published.<sup>3-6</sup>

The activity of nitrofurans is not confined to bacteria. Nitrofurazone and furazolidone are also active against certain protozoa of

TABLE 1: CHEMICAL NAMES AND STRUCTURES OF MEDICINAL NITROFURANS

<i>Common Name</i>	<i>Trade Name</i>	<i>Chemical Name</i>	<i>Chemical Structure</i> R is $\text{O}_2\text{N}-\text{C}_5\text{H}_3\text{O}-\text{CH}=\text{O}$
Nitrofurazone	'Furacin'	5-Nitro-2-furaldehyde semi-carbazone	$\text{R}=\text{N}-\text{NH.CO.NH}_2$
Nitrofurantoin	'Furadantin'	1-(5'-Nitro-2'-furfurylideneamino)-hydantoin	$\text{R}=\text{N}-\text{N}-\text{CO}$ $\text{CH}_2 \quad \text{NH}$ $\quad \quad \text{CO}$
Furazolidone	'Furoxone' 'Nefin' (Veterinary Grade)	3-(5'-Nitro-2'-furfurylideneamino)-oxazolid-2-one	$\text{R}=\text{N}-\text{N}-\text{CO}$ $\text{CH}_3 \quad \text{O}$ $\quad \quad \text{CH}_2$
Nifuraldezone	'Furamazone'	5-Nitro-2-furaldehyde semi-oxamazone	$\text{R}=\text{N}-\text{NH.CO.CO.NH}_2$
Nifuroxime	'Micofur'	5-Nitro-2-furaldehyde anti-oxime	$\text{R}=\text{N}-\text{OH}$

which species of *Eimeria* (nitrofurazone) which cause coccidiosis in fowls and other animals, and species of *Histomonas* (furazolidone) which cause hexamitiasis in fowls, are important. 'Micofur' is especially active against *Candida* (*Monilia*) *albicans* and many pathogenic fungi. 'Furaspor,' 5-nitro-2-furfuryl-methyl-ether, is also active against numerous pathogenic fungi.

#### CHEMICAL STRUCTURE AND ANTI-MICROBIAL ACTIVITY IN NITROFURANS

Exact correlations between chemical structure and anti-microbial activity cannot be made for nitrofurans so far. However, the following generalizations may be made.

1. The 5-nitro-furan group, as a whole, confers the overall activity.

TABLE 2: THE IN VITRO ANTIBACTERIAL SPECTRA OF NITROFURANS

Organism	Minimum Inhibitory Concentration (mg. % per 24 hours)				
	Nitrofurazone	Nitrofurantoin	Furazolidone	Furamazone	Micofur
<i>Aerobacter aerogenes</i> .. ..	1.4	2—<10	0.05—1.74		
<i>Alcaligenes faecalis</i> .. ..		<0.6			
<i>Bacillus anthracis</i> .. ..	0.6—1.0		0.04—0.13		
<i>Brucella abortus</i> .. ..	0.2—0.4	<0.6	0.5—0.67	2.0—3.7	<0.2—<1.0
<i>Brucella suis</i> .. ..	10.0		2.42—5.35		2.0
<i>Clostridium</i>					
<i>botulinum</i> .. ..			0.02		
<i>histolyticum</i> .. ..	<1.0		0.01		
<i>perfringens</i> .. ..	10.0		0.02		
<i>septicum</i> .. ..	<1.0		0.05		
<i>tetani</i> .. ..	5.0		0.01		
<i>Escherichia</i> .. ..	<0.6—1.0	<0.31—1.4	0.05—0.08	0.5—4.0	0.4—<1.6
<i>Klebsiella pneumoniae</i> .. ..	0.5—1.0	<0.6	0.09—0.18		
<i>Neisseria catarrhalis</i> .. ..	1.0				
<i>Neisseria gonorrhoeae</i> .. ..	1.0				
<i>Proteus mirabilis</i> .. ..		2.5	1.45		
<i>morganii</i> .. ..	4.0	2.5	1.10—1.95		
<i>rettgeri</i> .. ..		2.5	1.45		
<i>vulgaris</i> .. ..	2.0—6.0	1.25—10.0	1.05—4.85	4.4	3.1—12.5
<i>Pseudomonas</i>					
<i>aeruginosa</i> .. ..	>8.0	>10.0	1.59—>10.2	>5.0	12.3—32.3
<i>fluorescens</i> .. ..	>20.0				
<i>oleovorans</i> .. ..	4.6				
<i>putrefaciens</i> .. ..	0.6				
<i>syringae</i> .. ..		13.4			
<i>Salmonella</i>					
<i>cholerae suis</i> .. ..	0.5	0.5	<0.11—0.17	0.7—3.4	<0.2—3.0
<i>enteritidis</i> .. ..	0.8	1.29	<0.08—0.47		0.5
<i>gallinarum</i> .. ..	0.05—0.7		<0.02—0.44		
<i>ser. pullorum</i> .. ..	0.02—0.1		<0.02—0.38		
<i>paratyphi</i> .. ..	0.4	1.3	0.07—<0.1	1.5—3.7	0.5
<i>typhimurium</i> .. ..	0.8	1.44	0.08—0.17	3.7	0.5
<i>typhosa</i> .. ..	0.5—0.8	1.0—2.0	0.06—0.2	0.9—4.0	<0.2
<i>Shigella</i>					
<i>dysenteriae</i> .. ..	0.4	0.4	0.16	1.5	1.0
<i>species</i> .. ..	0.4	0.8	0.05—0.16	1.5	0.5
<i>sonnei</i> .. ..			0.04—0.08		
<i>Staphylococcus</i> sp. .. ..	<0.5—1.0	0.62—1.33	0.08—0.50	<0.5—3.0	<1.5—6.3
<i>Streptococcus</i>					
<i>agalactiae</i> .. ..	0.5—12.0	2.7—3.0	4.55—10.2	5.0	14.8—63.5
<i>uberis</i> .. ..	1.0—2.0	1.0—1.3			13.0
<i>faecalis</i> .. ..	>20.0	10.0	1.21	>5.0	
<i>pyogenes</i> .. ..	1.3	0.47—0.8	1.0—2.0	0.8—>4.0	0.5—3.4
<i>Vibrio comma</i> .. ..			<0.09		
<i>fetus</i> .. ..	<0.7		0.0025—0.03		<0.8

The activity of nitrofurans is not confined to bacteria. Nitrofurazone and furazolidone are also active against certain protozoa of which species of *Eimeria* (nitrofurazone) which cause coccidiosis in fowls and other animals, and species of *Histomonas* (furazolidone) which cause hexamitiasis in fowls, are important. 'Micofur' is especially active against *Candida* (*Monilia*) *albicans* and many pathogenic fungi. 'Furaspor,' 5-nitro-2-furfuryl-methyl-ether, is also active against numerous pathogenic fungi.

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1. "Triamcinolone  
in the treatment of rheumatoid  
arthritis." J. Amer Med Ass.  
167:973 (June 21) 1958



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Replacement of the 5-nitro-group with H-, Cl-, Br-, NH<sub>2</sub>-, etc. leads to much lowered activity, as does replacement of the furan ring with thiophene or pyrrole.<sup>7</sup> Derivatives of other nitro-aldehydes have also been shown to be inactive.<sup>8</sup>

2. The nature of the 2-substituent determines the degree of activity, the detailed spectrum of activity and the *in vivo* activity.

Most 2-substituted-5-nitro-furans exhibit marked anti-bacterial and/or anti-fungal activity *in vitro*. However, for marked activity *in vivo* the choice of 2-substituent is more restricted.

It appears desirable at this point to distinguish between nitro-furan and nitro-benzene derivatives. It is well known that the latter and the corresponding amino derivatives can cause serious blood dyscrasias. However, nitro-furans are much less stable than the corresponding nitro-benzene derivatives and their biologically reduced end-products, the 5-amino-furans are frankly unstable; indeed they are exceedingly difficult to prepare since the furan ring opens readily. Accordingly, blood dyscrasias of the kind due to other nitro-compounds would not be expected and have not been reported.

#### MODE OF ACTION OF NITROFURANS

Although nitrofurans have been shown to affect several enzyme systems, their precise mode and locus of action are not known. However, the mode of action is known to be different from that of other anti-bacterial agents and this accounts for the usefulness of nitrofurans in the treatment of infections due to antibiotic-resistant organisms. Most of the experimental work has been carried out with nitrofurazone which has been shown to interfere with the action of tissue dehydrogenases;<sup>11</sup> to be reduced by sensitive organisms;<sup>9, 10, 12-14</sup> to reduce the activity of bacterial dehydrogenases and so reduce oxygen uptake and glucose utilization;<sup>15, 16</sup> to affect the xanthine oxidase system and interfere in the Krebs' carbohydrate cycle.<sup>17</sup> It is not known which, if any one, of these is the critical action.

#### CLINICAL USES OF NITROFURAZONE

**Nitrofurazone.** Nitrofurazone is used mostly for local bacterial infections. A soluble ointment which contains 0.2% nitrofurazone in a water-soluble polyethylene glycol base is a

convenient preparation. Nitrofurazone is effective in the control of infection in accidental and surgical wounds, burns, varicose ulcers, bed sores and in skin-grafting operations. It is also very effective for the treatment of impetigo, infectious eczematoid dermatitis and similar superficial infections. For good results in deep-seated infections, surgical incision and drainage are necessary before the infected area is irrigated or packed with a nitrofurazone dressing. Nitrofurazone in the form of vaginal or urethral suppositories is used for bacterial infections of the uro-genital tract, such as urethritis and vaginitis and for the prevention and suppression of infections in the vaginal tract after surgery, radiation, etc. In all these applications nitrofurazone usually controls infection rapidly and allows natural granulation of the wound and growth of new epithelium. The only major side effect attending its use is dermatitis in a few sensitive persons, when the drug should be stopped and anti-histamine drugs given. The dermatitis usually clears quickly.

Nitrofurazone has no common systemic use in Man but has been used experimentally in trypanosomal infections<sup>18</sup> and with some success in the treatment of testicular seminoma.<sup>19, 20</sup> However, systemic administration of the drug may cause severe peripheral neuritis requiring that treatment be stopped.

**Nitrofurantoin.** The main use of nitrofurantoin is as a urinary tract antiseptic. About 40-50% of orally ingested nitrofurantoin is excreted rapidly in the urine, where concentrations as high as 30-40 mg. per 100 ml. may be obtained. *In vitro* solubility of nitrofurantoin in urine at 37° C. is about 22.5 mg. per 100 ml. at pH 5 and increases rapidly above pH 6, due to the formation of a soluble anion, since the drug is an acid. However, the drug easily forms rather stable super-saturated solutions. For example, at 37° C. at pH 5 solutions containing up to 4 times the maximum *in vitro* solubility did not precipitate after 6 days' storage. Accordingly, crystalluria is not a problem with nitrofurantoin.<sup>5</sup> Nitrofurantoin has been shown to be more effective in slightly acid urine,<sup>21</sup> probably because the undissociated drug is required to penetrate the bacterial cells before the anti-bacterial effect is obtained. From the anti-bacterial spectrum, it is evident that nitrofurantoin is effective against many organisms commonly found in urinary tract infections. It is especially useful for *Proteus* infections. The average dose is

about 7 mgm. per Kg. per day administered as tablets in 4 divided doses.

Nitrofurantoin, being rapidly excreted and therefore not giving effective blood or tissue concentrations, is not normally effective in systemic infections when administered by mouth. However, administered intravenously in saline or glucose saline, it has proved to be life-saving in generalized infections caused by organisms resistant to antibiotics.<sup>22</sup>

The main side effects caused by nitrofurantoin are nausea and vomiting and, in a few cases, skin rash. However, care should be exercised when administering the drug to negro patients since it has been known to cause mild haemolytic anaemia in a few congenitally susceptible subjects. In this respect, it is similar to primaquine, acetanilide and several other currently used drugs.<sup>23</sup>

*Furazolidone.* Until recently the main use for furazolidone was in trichomonal vaginitis. The drug was administered in water-miscible vaginal suppositories and vaginal powder. An improved product is now available in the same forms but which contains both furazolidone and Micofur, the former to deal with trichomonal infection and the latter with concurrent monilial infection. Recently, however, it has been shown that furazolidone is effective in dysentery and diarrhoea of bacterial origin.<sup>24-26</sup> From the anti-bacterial spectrum it is evident that *Salmonella* and *Shigella* species and *E. coli*, common causal organisms, are very sensitive to the drug. For intestinal tract infections furazolidone is administered in tablets or as an aqueous suspension containing, in addition, kaolin and pectin as adjuvant secondary drugs. The average adult daily dose is about 400 mg. given in 4 divided doses. Furazolidone has also been shown to have a hypotensive effect in humans when given over longer periods but it appears that side effects might make this result of academic interest only.<sup>27</sup> No serious side effects have been reported from the use of furazolidone in trichomonal vaginitis or intestinal tract infections. Skin rashes might be expected in some sensitive individuals and, perhaps, nausea.

*Furamazone.* So far furamazone has not found a place in human medicine.

#### THE FUTURE AND NITROFURANS

As yet, the nitrofurans, useful and important as they are, have been used mostly for localized infections. Clearly, however, drugs with

such a wide spectrum of anti-bacterial activity and with a mode of action different from other anti-bacterials must be of value in systemic infections if adequate blood and tissue concentrations could be achieved for satisfactory periods. The results obtained with intravenous nitrofurantoin confirm this view. Unfortunately, the nitrofurans now available apparently cannot be relied upon to provide such concentrations when taken by mouth, although the margin of default must be small since the compounds can cure experimentally infected mice and there is evidence that furazolidone, e.g. when used for the treatment of dysentery, has caused significant improvement in chronic bronchitis.<sup>27</sup> Because of this evidence, it appears highly probable that a systemically active nitrofurantoin will be developed. The established nitrofurans fail either because of low solubility and slow absorption or because of rapid excretion. Less polar nitrofurans might be excreted more slowly but yet be absorbed readily and it would appear possible to discover such a compound.

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## REVERSIBLE FAILURE IN CARDIO-RESPIRATORY DISEASE

### A CASE REPORT

P. LEFTWICH, B.Sc., M.R.C.P. (LOND.)

*Cape Town*

Congestive cardiac failure has (apart from obvious nutritional and metabolic cardiopathies or congenital and valvular abnormalities amenable to surgical correction) a progressive course, responding to a greater or lesser degree to medical treatment, but not remitting to a point at which complete recovery ensues and treatment by drugs or restriction of activity is no longer necessary. Exceptions to this rule may occur in cardio-respiratory failure in patients with grossly deformed chests, and also in excessively obese subjects.

In their classical article on what they called 'pulmono-cardiac failure' in patients with severe chest deformity (a contribution in this field which has hardly been bettered since) Chapman *et al.*<sup>1</sup> related the case histories of 12 patients with severe kyphosis, scoliosis, kyphoscoliosis, and pectus excavatum resulting in gross deformities of the chest, and described varying degrees of heart involvement; but only a single patient in the series developed congestive failure. Symptoms of cardiac failure had been ascribed previously to dislocation of the heart or bending of the great vessels in the thorax, but in their view it was more likely due to an actual reduction in lung volume with resulting chronic anoxaemia. They found no increased CO<sub>2</sub> retention or appreciable reduction in the arterial oxygen saturation. In the (then) absence of sulpha and antibiotic drugs, they found the prognosis for long life poor.

Hanley *et al.*<sup>2</sup> recently reported the results of their study of 24 hunchbacks, 16 of whom suffered from congestive failure. Their results differed from those of Chapman *et al.* inasmuch as those patients who had been in congestive failure tended to have a low arterial oxygen saturation and a raised CO<sub>2</sub> tension. The

lungs of the hunchback tended to be evenly ventilated and there was no bronchial obstruction, as is found in the subjects of chronic bronchitis and emphysema. They could find no definite evidence of pulmonary hypertension in the few cases studied by cardiac catheterization, but raised the possibility that acute episodes of bronchitis might increase the pulmonary artery tension and precipitate failure.

The patient described in the following case history had a deformed chest and suffered 2 attacks of severe congestive cardiac failure at an interval of 8 years, but remained in good health without active treatment between the attacks. Several factors in the management of this syndrome are discussed.

### CASE HISTORY

H. S., an active business man, was seen for the first time in 1950, aged 46 years. He had had a gross deformity of the chest since childhood, and had always been slightly dyspnoeic, but he could walk long distances without distress. He was a heavy smoker and had noticed a steady increase in weight for several years before. For 3 months past he had experienced increasing dyspnoea and for 3 weeks there had been swelling of the feet and abdomen.

He was a cyanotic, short-statured man measuring 4 ft. 10 in. in height and weighing 150 lb. There was marked high right kyphoscoliosis. The head was low between the shoulders and the lower ribs almost touched the brim of the pelvis. The blood pressure was 170/105 mm. Hg. A triple rhythm was heard over the praecordium. There was neck vein distension, with moist sounds at the lung bases, ascites and sacral and ankle oedema.



X-ray screening showed the heart to be occupying the left hemi-thorax and there was marked reduction in the area of lung trans-radiancy. The cardiograph tracing was difficult to interpret both as to the position and the intrinsic status of the heart. The blood proteins were normal and the urine contained a trace of albumin.

With conventional treatment by means of bed rest, digitalis and mercurial diuretics, signs of congestive failure disappeared over a period of 6 weeks. His weight fell to 133 lb. on a simple reducing diet and he stopped smoking. All treatment was then discontinued. The life-long habitual slight dyspnoea remained, but he was able to resume normal business activities and undertook a crowded overseas holiday, entailing much walking without strain. In 1952 a duodenal ulcer perforated and the operation was well tolerated.

He continued to enjoy reasonably good health until September 1958, more than 8 years after the original attack of congestive failure. During the previous year he had relaxed precautions about his diet and had gained 15 lb. in weight. Dyspnoea had gradually increased and he displayed signs of cardiac failure, almost identical with those seen 8 years before. He was now mildly polycythaemic, the haemoglobin being 17.5 g. % and the red cell count 6,400,000 per c.mm.; the alkali reserve was normal. The cardiograph was once again difficult to interpret, but was more suggestive of left than right heart damage.

Following intermittent oxygen inhalation, digitalis, Chlortride, and a rigid reducing diet, as well as tetracycline to combat possible sepsis, he made rapid improvement and lost all signs of congestion. Six weeks later his weight was down to 135 lb. and he was able to resume his normal activities. He has remained in good health for the past 7 months and has required no treatment during this time.

#### DISCUSSION

The importance of weight reduction in the control of cardio-respiratory disease in patients with deformed chests is well shown in the medical history of this case. In recent years increasing interest has been taken in the syndrome of heart failure in the obese, both with normal and abnormal lungs. Its features have been described by Burwell *et al.*<sup>3</sup>, Lillington *et al.*<sup>4</sup>, Kaufman *et al.*<sup>5</sup>, and others. It has been shown that in excessively obese patients with normal lungs, a high proportion show low arterial oxygen saturation, retention of CO<sub>2</sub>

and varying degrees of polycythaemia. The clinical manifestations are fatigue, drowsiness, dyspnoea and cyanosis and, in occasional cases, right-sided congestive heart failure.

Tests of pulmonary function by many workers point to diminished alveolar ventilation leading to chronic anoxaemia as the immediate cause of the syndrome, but the exact mechanism whereby obesity brings this about is not clear. Respiratory movements are impeded by the cuirasse effect of fat surrounding the chest wall and also by interference with freedom of movement of the diaphragm by accumulation of fat in the peritoneal cavity. The increased effort required to carry out regular full respiration in the obese finally results in shallow and inefficient alveolar ventilation.

In kyphoscoliotic subjects the total lung capacity may be reduced to as little as a quarter of the normal. The chest wall tends to be rigid and breathing is largely abdominal. These patients live under the constant threat of heart failure and any additional handicap to proper ventilation, such as obesity or lung infection, however slight, may be sufficient to precipitate circulatory failure. Life-long care about diet and the periodic use of antibiotics to minimize the risk of lung sepsis are essential for prolongation of life of the patient with severe deformity of the chest.

#### SUMMARY

The clinical features and mechanism of reversible cardiac failure in a hunchback are described.

The importance of weight reduction and the control of lung infection in this condition are outlined.

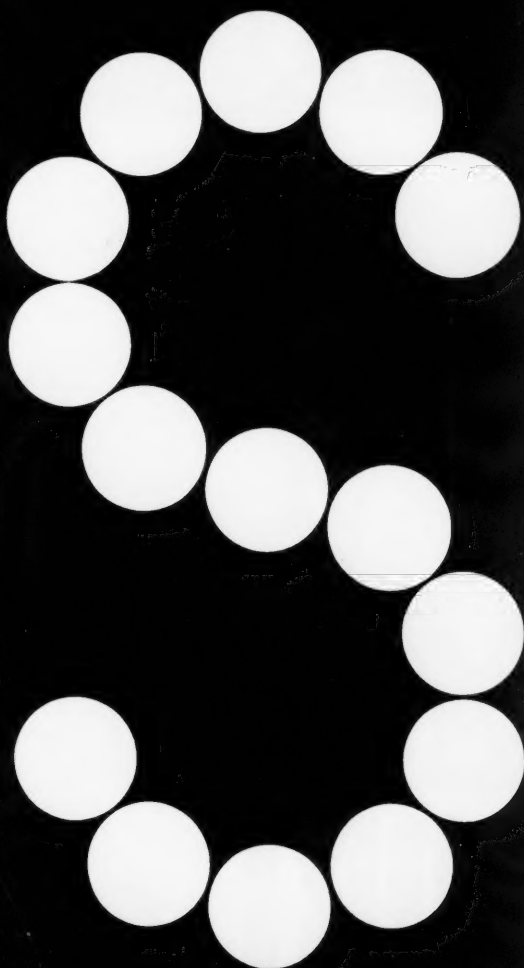
#### OPSOMMING

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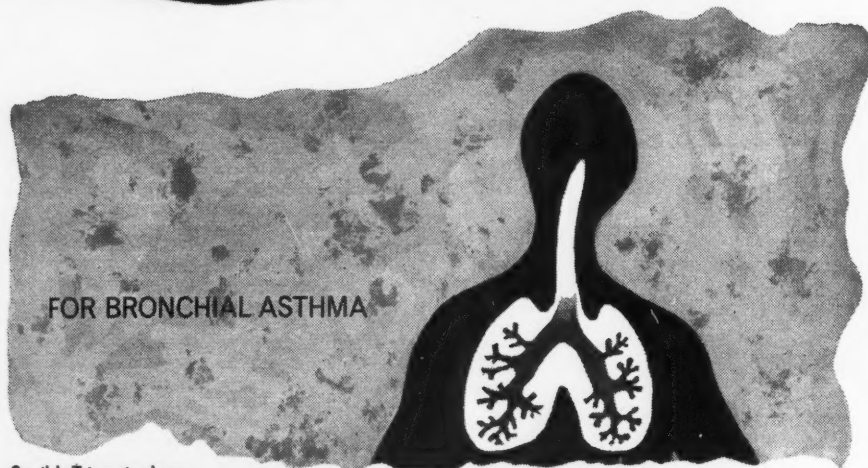
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## MEDICO-LEGAL SECTION

## MEDICAL NEGLIGENCE: X-RAY BURN

*Lymbery, Appellant v. Jefferies, Respondent\**

(Bloemfontein—Cape Town)

(1924. October 15. 1925. January 12. INNES, C.J.; SOLOMON, J.A.; DE VILLIERS, J.A.; KOTZE, J.A.; WESSELS, J.A.)

*Negligence.*—Medical Practitioner.—Patient sent to radiologist for treatment.—Duty of practitioner.—Qualifications of radiologist.—Whether radiologist exercising calling of medical practitioner.—Ordinance 29 of 1904 (T) section 39.—Liability of practitioner for acts of radiologist.

The appellant a married woman instituted an action for damages against the respondent a medical practitioner on the ground that through his negligence in sending her to one E., an unqualified X-ray operator at a certain hospital, she was burnt whilst undergoing treatment there. It appeared that the appellant consulted the respondent with regard to a certain complaint. After unsuccessful surgical treatment the respondent advised her to undergo a deepseated X-ray treatment at a certain hospital. The respondent was not skilled in the application of X-rays and had to rely upon others to perform the actual treatment. The evidence showed that a great number of doctors sent their patients to the hospital in question to be there treated by E., who was in charge of the X-ray department. It was their practice to indicate to E. for what purpose the patient was sent and there he applied the X-rays. In the present case the respondent followed that practice and the appellant presented herself at the hospital and was subjected to the X-rays. As a result of this treatment the appellant was severely burnt and suffered in consequence a great deal of pain and discomfort. After the burn manifested itself she was for a long time treated by the respondent and eventually the trouble was mitigated by skin grafting. The respondent did not himself take any part in the actual X-ray treatment. This was left entirely to E.

The appellant contended that the respondent had been negligent in the following respects: (1) That the respondent had not informed her that she would become sterile as a result of the treatment; (2) that he did not inform her that the treatment was a dangerous one; (3) that after she complained to the respondent that the treatment was producing a rash he negligently told her to continue it; (4) that the respondent sent her to be treated by E. when he knew full well that E. was not a legally qualified radiologist, but at most only a radiographer; that E. treated her negligently and therefore the respondent was in law responsible for the damages she had suffered. A trial Court having given judgment for the respondent.

*Held*, dismissing an appeal, that on the facts, grounds (1) and (3) relied upon could not be supported.

*Held*, further, that as to ground (2) there was no duty in the circumstances imposed upon the respondent to inform the appellant that a burn might result from the X-ray treatment as the evidence showed that as a rule no danger attended the particular treatment ordered by the respondent and that burns were rare in such a case and often due to some idiosyncrasy on the part of the patient which could not be foretold.

*Held*, further, that in the circumstances of the case E. was not the agent of the respondent and that respondent was not liable on that ground for the acts of E.

*Held*, further, that on the evidence E. was well qualified to administer the treatment ordered and that the respondent had not been negligent in sending the appellant to E. for treatment without being present himself during the application of the treatment.

*Held*, further, that as E. as an X-ray operator diagnosed nothing, nor suggested any treatment, but merely carried out the instructions of a medical man, he could not be said to have performed an act specially belonging to the calling of a medical practitioner and that the respondent could, therefore, not be liable for the negligence of E. on the ground that E. had, to the knowledge of respondent, exercised the calling of a medical practitioner in contravention of Ordinance 29 of 1904 (Transvaal) sec. 39.

The decision of the Transvaal Provincial Division in *Lymbery v. Jefferies* confirmed.

Appeal from a decision of the Transvaal Provincial Division (Stratford, J., and Feet-ham, J.).

The plaintiff in the court below claimed damages from the defendant, a medical practitioner, on the ground of alleged negligence in sending her to an unqualified X-ray operator. The Trial Court gave judgment for the defendant and the plaintiff now appealed.

O. Pirow, K.C. (with him G. G. Maritz) for the appellant: The defendant is liable because, whilst himself ignorant of any details of X-ray treatment he handed over a patient to one not qualified to administer treatment, which treatment, owing to the negligence of the person administering it, resulted in the injury complained of. See Beven on Negligence (3rd ed., Vol. 2, p. 1160). *Pharmaceutical Society v. Wheelodon* (L.R. 24 Q.B.D. 683, at p. 690). All the time that the patient is under the treatment of an unqualified man he remains the patient of a medical practitioner. There must,

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at any rate, be *direct* medical control. See *Rex v. Foster* (1917, T.P.D. 38).

The treatment is an act specially belonging to the calling of a medical practitioner. See sec. 39 of Ordinance 29 of 1904 (T). *Rex v. Greene* (1905, T.S. 595); *Rex v. Smith* (1917, T.P.D. 206, at p. 209, per Bristowe, J.).

The object of the legislature's insistence on qualification is the protection of the public. See *Rex v. Foster* (*supra*). Beven on Negligence, p. 1160 (footnote).

Defendant is liable because either through ignorance or neglect he advised X-ray treatment without telling the plaintiff one or all of three things: (1) That the radiographer was not legally qualified to administer the treatment. (2) That even if successful the treatment would have certain injurious effects. (3) That such treatment was attended with a probability of danger—even death.

This absence of warning is negligence and possibly assault, because of the absence of consent. See *Salter v. Baker & Stapleton* (2 Wilson K.B. 359 and 95 English Reports 860).

The treatment being in an experimental stage another element of danger is added. See Beven on Negligence, p. 1158.

A. Davis, K.C. (with him N. C. B. Price) for the respondent: The duties of a radiographer do not specially pertain to the calling of a medical practitioner. See *Rex v. van der Heim* (1914, T.P.D. 434) as the work is purely mechanical. Taking photographs is as dangerous as treatment. *Runyan v. Goodrum* (13 American L.R. (Annotated) 1403, at p. 1405); *Siemens v. Turner* (117 Atlantic Reports 922); International Abstract of Surgery (August, 1923, p. 120). Ensor was certainly not defendant's agent.

The *onus* is on plaintiff to prove negligence. This is not a case of *res ipsa loquitur*. See *Coppen v. Impey* (1916, C.P.D. 309); *Van Wijk v. Lewis* (1924, A.D. 438). Medical supervision would have been quite useless. There should have been some evidence for the inference that if the explanations as to the danger of the treatment had been given she would have refrained from the treatment.

Pirrow, K.C., replied.

Cur. adv. vult.

*Postea* (January 12th).

Wessels, J.A.: The appellant, a married woman, instituted in the Transvaal Provincial Division an action for damages against the respondent, a medical practitioner, on the ground that through his negligence in sending her to Mr. Ensor, an unqualified X-ray operator

at the Pretoria Hospital, she was burnt whilst undergoing treatment there. The Court decided in favour of the respondent and from this judgment the appellant now appeals.

The facts are briefly as follows: Mrs. Lymbery, the appellant, consulted Dr. Jefferies with regard to flooding to which she was subject. He diagnosed fibrosis of the uterus and after unsuccessful surgical treatment he advised her to undergo a deep-seated X-ray treatment at the Pretoria Hospital. Dr. Jefferies is not skilled in the application of X-rays and has to rely upon others to perform the actual treatment. The evidence shows that a great number of the doctors practising at Pretoria send their patients to the Pretoria Hospital to be there treated by Mr. Ensor who is in charge of that department. It is their practice to indicate to Mr. Ensor for what purpose the patient is sent and then he applies the X-rays.

In this case Dr. Jefferies informed Mr. Ensor that Mrs. Lymbery was suffering from fibrosis of the uterus and that he wanted Ensor to give her a course of X-ray treatment for the complaint. He also gave Mrs. Lymbery a note to that effect to present to Mr. Ensor. In due course Mrs. Lymbery presented herself at the Hospital and was subjected to the X-rays. As a result of this treatment the appellant was very severely burnt and suffered in consequence a great deal of pain and discomfort. After the burn manifested itself she was for a long time treated by Dr. Jefferies and eventually the trouble was mitigated by skin grafting. The respondent did not himself take any part in the actual X-ray treatment. This was left entirely to Mr. Ensor.

In her action she complains that her pain and suffering was due to the negligence of Dr. Jefferies and that he is responsible for the injury done to her by what she considers the unskilful treatment of Ensor.

The acts of negligence complained of and attributed to the respondent may be classified as follows:

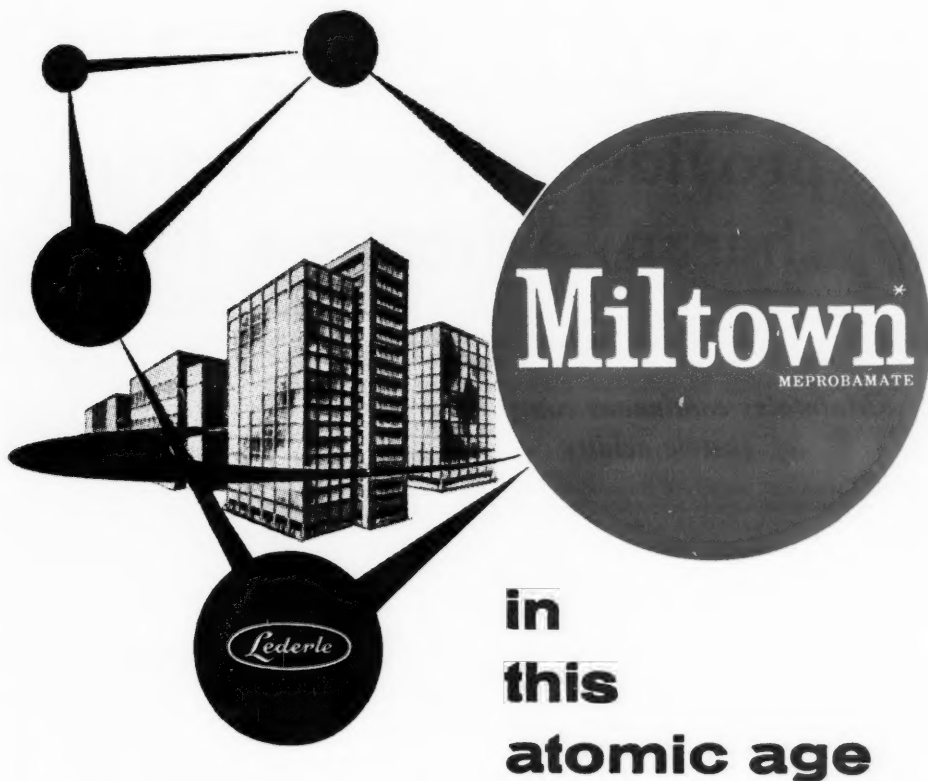
(1) Dr. Jefferies did not inform the appellant that one of the consequences of the X-ray treatment for fibrosis uteri was that her ovaries would be destroyed and in consequence she would be rendered sterile.

(2) That he did not inform her that the treatment is a dangerous one which might cause pain and suffering.

(3) That after she complained to the respondent that the treatment was producing a rash he negligently told her to continue it.

(4) The respondent sent her to be treated at the Pretoria Hospital by Mr. Ensor when he knew full well that the latter was not a legally



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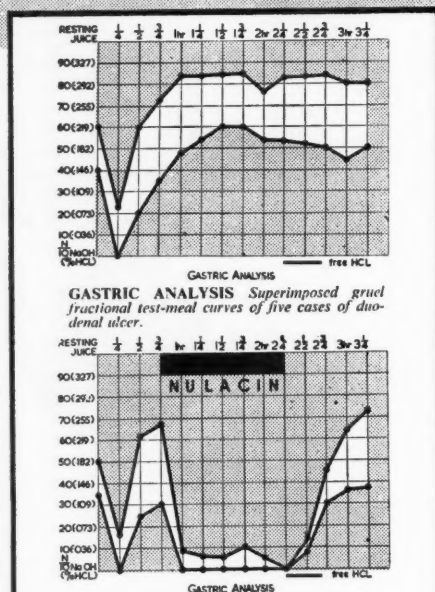
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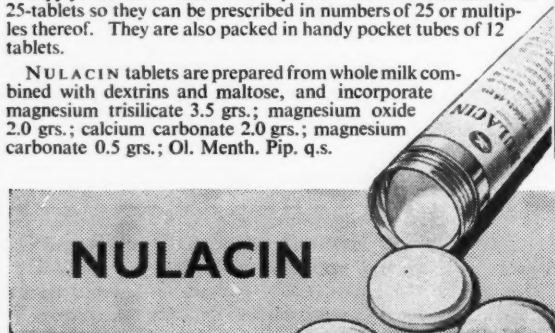
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## BIBLIOGRAPHY

- Practitioner*, 1957, **178**: 43  
*Practitioner*, 1956, **176**: 103  
*Amer. J. Gastro.* 1956, **26**: 665  
*Brit. Med. J.* 1954, **1**: 46

Further references to the literature and full information on Nulacin available on request.



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qualified radiologist, but at most only a radiographer. That Ensor treated her unskilfully and negligently and therefore the respondent is in law responsible for the damages she has suffered.

We may clear the ground by disposing at once of some of the appellant's contentions.

It was argued that Dr. Jefferies ought to have informed his patient of the fact that she would become sterile. The learned Judge in the court below found as a fact that Dr. Jefferies did tell her that she would not see her menstrual periods again. There is no reason for questioning this finding. The respondent is a middle aged woman and must have understood that this meant that she would not be capable of bearing children after the treatment. This ground of complaint therefore falls away.

The next ground of negligence may also be disposed of viz.: that the respondent did not point out clearly the dangers to which the appellant might be exposed from submitting to the X-ray treatment. It was argued that it was negligence on the part of a surgeon or doctor not to inform his patient of the danger of an operation or treatment.

It may well be that it is the duty of a surgeon before operating to tell the patient that the operation is dangerous and may end in death, or that it will be accompanied with great pain, and to obtain the patient's consent. In such cases, however, all the surgeon is called upon to do is to give some general idea of the consequences. There is no necessity to point out meticulously all the complications that may arise.

Now the evidence of Dr. Steuart, a qualified radiologist and demonstrator in radiography at the Witwatersrand University, is that there is no need to warn a patient of the danger of submitting to X-ray treatment for fibrosis of the uterus because as a rule there is no danger attending this treatment. The evidence shows that burns are rare where the treatment is properly carried out and often due to some idiosyncrasy on the part of the patient which cannot be foretold. I am therefore of opinion that no duty was imposed upon Dr. Jefferies to point out to Mrs. Lymbery that a burn might result from an X-ray treatment for fibrosis uteri.

The third ground of negligence was not pressed and it is clear from the evidence that when she consulted Dr. Jefferies after the treatment the injury had already been inflicted though the symptoms had not then manifested themselves. The medical treatment adopted by Dr. Jefferies after the burn was caused has

met with the approval of the other practitioners called and there is no evidence whatever of any negligence on his part in the treatment he then adopted.

This brings us to the really important question which arises in this case. Was it negligence on the part of Dr. Jefferies to send his patient to the Hospital to be treated for fibrosis uteri by means of X-rays when he knew that the operator was not a qualified medical practitioner and not a radiologist? If Ensor was negligent is Dr. Jefferies under the circumstances of the present case liable for the injury caused to the appellant by Ensor?

In the court below it was contended that Ensor was the agent of the respondent and that, therefore, the latter was responsible for the alleged negligence of Ensor. It is, however, quite clear that the learned Judge in the court below was correct in holding that Ensor was not the agent of the respondent.

If a medical practitioner or surgeon advises his patient to be treated by some third person, either because it is a treatment which he cannot carry out himself or which it is customary to entrust to a third person, then the latter does not as a general rule act as the agent of the medical practitioner or surgeon. This principle is the basis of the decision of *Perionowsky v. Freeman* (4 F. & F., p. 977). In the recent case of *Lewis v. van Wijk* this Court held that a surgeon was not responsible for the mistake of a Head Sister in counting the swabs used at an operation, as this was her special duty, even though she was throughout under the general control of the operator.

It has been urged that we are dealing here with an exception to the general rule because Ensor is not a qualified radiologist and because our Statute Law forbids Ensor, not being a qualified radiologist, to carry out the treatment he did, for in subjecting Mrs. Lymbery to the X-ray treatment he did an act such as specially belongs to the calling of a medical practitioner. (Ordinance 29 of 1904 sec. 39). Ensor must, therefore, be regarded in this case as the assistant or agent of Dr. Jefferies.

It appears from the evidence that there is a distinction between a radiologist and a radiographer. The former is a medical practitioner who has also studied electricity and the application of electrical processes to therapeutics. He diagnoses the case and prescribes electrical treatment and usually himself subjects the patient to the required electrical process, or else he applies electrical treatment at the request of another practitioner. A radiographer is a layman who has had adequate training in X-ray work. There is no special

examination in the Union either for radiologists or radiographers.\* Dr. Louw, the Superintendent of the Pretoria Hospital, who has some special knowledge of X-ray work in connection with miners' phthisis, states that there are only three radiologists known to him in the Transvaal and they are all at Johannesburg. Two of them are in partnership. According to his evidence there is no X-ray expert in Pretoria except Mr. Ensor; he is regarded by the Hospital staff as such. Dr. Sanders and Dr. Troup, two well-known Pretoria doctors, regard Mr. Ensor as an X-ray expert and have entrusted numbers of their patients to his care. It is quite clear that Mr. Ensor possessed no diploma either as radiologist or radiographer at the time when he treated Mrs. Lymbery. He was a member of the Rontgen Society though that society issues no diploma. After his treatment of Mrs. Lymbery he became, in January, 1923, a member of the Society of Radiographers on his local service at the Pretoria Hospital. It appears from the evidence of Mr. Ensor, and there is no reason to doubt the correctness of his evidence, that he had some eight years experience as an electrician in New Zealand before he came to this country. In 1902 he was a patient at the Pretoria Hospital, and when Dr. Thornton, the then Superintendent of the Pretoria Hospital, installed an X-ray plant there, Ensor interested himself in the matter and under Dr. Thornton began to study the working of the apparatus and to read up the subject. In 1910 the Pretoria Hospital installed an up-to-date X-ray plant and Ensor was placed in charge of that department, though the work was only carried on from five o'clock in the afternoon to late at night. In 1911 he started with simple cases of X-ray therapy, increasing his work as he increased his knowledge and experience. In 1917 he was appointed full time radiographer to the Hospital. He tells us that as radiographer he has had some 16,000 cases, and of those between 2,000 and 3,000 were therapeutical cases. He has studied anatomy and knows so much of the subject that if a doctor tells him that he wants treatment of a particular disease he knows exactly how and where to apply the X-rays. Sometimes a doctor who sends patients to him may be in attendance, but in the majority of cases the doctor merely informs him what the treatment is for and does not personally attend. He never treats patients unless they are sent to him by a medical man.

Dr. Sanders has stated in evidence that he

has some knowledge of radiography and that, in his opinion, Mr. Ensor is an exceedingly good X-ray operator: "I think he is quite efficient, and I think he is a man who endeavours by every possible means to make and keep himself as efficient as a man can be." Dr. Sanders was not in the habit of being present when his patients were being treated by Ensor. He says: "When I sent those cases I either wrote a short note to Mr. Ensor telling him what is the matter with the patient and asking him to treat the patient with X-rays, or I rang him up over the telephone and told him about the case. If I wanted a patient treated for fibrosis of the uterus I should simply tell him that she was suffering from fibroid tumour or fibrosis of the uterus and ask him to adopt the usual treatment."

Dr. Troup's evidence is to the same effect. It was shown that Dr. Sthamer, who gave evidence for the appellant, adopted a similar course and simply sent a note to Mr. Ensor to tell him what the treatment was for. (Exhibit B). Amongst the cases sent by Dr. Sthamer was one for cancer which had broken out again after an operation.

Although, therefore, Mr. Ensor possessed no diploma at the time when he treated Mrs. Lymbery, yet he had had a long practical experience and, in the opinion of some of the principal medical practitioners of Pretoria, he was an expert X-ray operator to whom they could entrust their patients without scruple or fear. They regarded his anatomical knowledge so satisfactory that they merely indicated the disease for which the treatment was required and left the actual application of the X-rays to him.

In these circumstances was it negligence on the part of Dr. Jefferies to send Mrs. Lymbery to the Pretoria Hospital to be treated with X-rays for fibrosis uteri by Mr. Ensor without being present during the application? I cannot see upon what principle Dr. Jefferies can be said to have been negligent in that respect. The law does not require an X-ray operator to have any diploma any more than it requires a diploma for a masseur\* or for an instrument-maker, who is directed by a doctor, to fit a particular kind of boot to a foot. Not only does the hospital hold him out as qualified to do the work, but Dr. Jefferies, when resident medical officer at the Pretoria Hospital, saw Ensor's work as an X-ray operator, and knew his capacity and his qualification for doing the work. Many of the principal doctors of Pre-

\* Note: This judgment was delivered in 1925. Since then, the South African Medical Council has made provision for Voluntary Registers in connexion with Supplementary Health Services personnel, eg. radiographers and physiotherapists.—Editor.

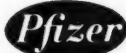


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toria recognized his capacity and sent their patients to him. The learned Judge in the court below came to the conclusion that Ensor was well qualified to administer the treatment and to know what to do when he was informed that the case was one of fibrosis uteri, and I see no reason to take any other view.

This, however, does not conclude the matter, for if the law forbids Ensor to carry out the treatment, however qualified he may be in fact, then Dr. Jefferies, who knew that Ensor had no diploma, may well be responsible for the negligent act of Ensor. Mr. Pirow contended that Ensor, in treating Mrs. Lymbery with X-rays, performed an act which specially belongs to the calling of a medical practitioner and this Ordinance 29 of 1904, sec. 39, forbids him to do.

It is difficult to lay down a general rule when and when not a person does an act which specially belongs to the calling of a medical practitioner.

If the section is interpreted narrowly it may prevent a person from alleviating the sufferings of his neighbour by advising the use of or administering some household remedy, or it might even prevent the administering of first aid; if interpreted too widely, it may open the doors to quackery. It has been decided that there can be no practice as a medical man if the person concerned neither diagnoses nor prescribes, but only treats as directed by another. We have, therefore, to adopt some middle course. Now Mr. Ensor as an X-ray operator diagnoses nothing; he does not suggest any treatment; he merely carries out the instructions of a medical man. It is true that he is left alone to direct the incidence of the

X-rays. The doctor does not say to him: "Direct the rays here or direct them there," but tells him to direct X-rays for a particular case, e.g. fibrosis uteri. Now if the doctor knows, as is the case here, that the operator is well aware of what he is to do when told to treat a case of fibrosis uteri, it seems to me waste of time and money for the doctor to accompany his patient and to point out to the operator how to direct the rays. This is all the doctor can do, because the evidence shows clearly that medical men, as a rule, are ignorant of the technique of radiography. The fact that the operator is left to himself to determine the dosage and the incidence of the X-rays does not bring him within sec. 39 of the Ordinance. He does not, by applying the standard dosage and directing the X-rays at the request of a medical man, perform an act which specially belongs to the calling of a medical practitioner. What he does is, upon the request of a doctor, to perform an act which specially belongs to the calling of a radiographer or person skilled in the use of X-rays, and the manipulation of an X-ray plant. This ground of appeal must, therefore, also fail.

It is, therefore, unnecessary to decide whether there was or was not negligence on the part of Mr. Ensor, though I see no reason to differ in that respect from the conclusion of the learned Judge in the court below.

The appeal must, therefore, be dismissed with costs.

Innes, C.J.; Solomon, J.A.; de Villiers, J.A., and Kotze, J.A., concurred.

*Appeal accordingly dismissed.*

## NOTES AND NEWS : BERIGTE

Mr. Derk Crichton, M.B., Ch.B., D.Phil., F.R.C.S., F.R.C.O.G., has commenced practice as a Specialist Obstetrician and Gynaecologist at 512 Sanlam Building, Smith Street, Durban. (Telephones: Rooms: 5-6679; 6-4626; Residence: 8-5580).

The telephone number and address of Mr. Jack Penn, F.R.C.S., (i.e. Clarendon Centre, 4 Park Lane, Parktown, Johannesburg, Telephone No. 44-9587) is unchanged, although this information has inadvertently been omitted from the recent Telephone Directory.

Dr. Wallace M. Levy, M.B., B.Ch. (Rand), D.O.R.C.P. (Lond.), R.C.S. (Eng.), formerly Ophthalmic Registrar, Johannesburg General Hospital, who recently returned from postgraduate study at the Institute of Ophthalmology and its associated hospitals, Moorfields, London, and various Ophthalmic Clinics on the Continent, has joined Dr. L. Staz in his practice as an Ophthalmic Surgeon, at 428 Lister Building, Jeppe Street, Johannesburg. Telephone: 22-6200 (Rooms); 54-2081 (Residence).

Dr. Louis F. Freed, F.R.S.S.Af., of Johannesburg, has been invited by Dr. Lucien Sylvestre, President of the Organizing Committee, to attend the *First Canadian Symposium on Non-Gonococcal Urethritis and Human Trichomoniasis*, to be held in Montreal on 21-22 September 1959.

Dr. Percy Reichman, M.B., B.Ch. (Rand), D.M.R.D., R.C.P. (Lond.), R.C.S. (Eng.), has joined Dr. E. Alan Price in Radiological Practice at 401 Medical Arts Building, corner of Jeppe and Troye Streets, Johannesburg. (Telephones: Residence: 44-4947; Rooms: 22-1735/6.)

Dr. P. Marchand has been awarded a Wellcome Research Grant for the purpose of further study of the techniques of open heart surgery in the U.S.A.

This award was first announced in South Africa in our editorial columns on 18 April 1959.

Dr. Marchand will take up the award early next year. He will be away for 3 months.

## PREPARATIONS AND APPLIANCES

RAUTRAX (FLUMETHIAZIDE) FOR HYPERTENSION  
A NEW ORAL DIURETIC

Synthesis of a new oral diuretic flumethiazide by scientists of the Squibb Institute for Medical Research has resulted in another step forward in the treatment of hypertensive disease.

Flumethiazide synthesized by Squibb has been combined with whole root *Rauwolfia serpentina* and gratifying results were obtained in the treatment of hypertension by various investigators. The combined product is called *Rautrax*.

Flumethiazide is an effective oral diuretic (saluretic) which induces excretion of potassium at a lower rate than other benzothiadiazine diuretics now in use. Potassium depletion may have adverse effects on heart action, particularly in congestive heart failure. It can also cause generalized muscle weakness and a feeling of lassitude, especially in long-term treatment where insidious potassium depletion may occur.



Flumethiazide potentiates the antihypertensive action of *Rauwolfia serpentina*. The combined product, *Rautrax*, provides flumethiazide for diuretic and antihypertensive effect, whole root *Rauwolfia serpentina* for tranquilizing and antihypertensive action together with supplementary potassium chloride. *Rautrax* is indicated in all patients with hypertension, particularly when there is less than optimal response to antihypertensive agents used, when greater or smoother reduction of blood pressure is desired, and in the presence of oedema or congestive heart

failure. It is particularly recommended for the anxious hypertensive patient.

**Subjective Improvement.** Authors reported almost complete relief of associated symptoms such as headache, dizziness and blurring of vision and the absence of serious or even unpleasant side effects. After periods of up to 4½ months, no tolerance to the antihypertensive action of *Rautrax* was observed.

The potentiating effect permits lower dosage regimens when *Rautrax* is used. Similarly, for patients receiving other antihypertensive therapy, Squibb recommends reduced dosage upon institution of *Rautrax* treatment.

**Side Effects.** With *Rautrax* treatment these have been minimal, rarely warranting discontinuation of medication. Neither gout nor hepatic coma, observed with other benzothiadiazine diuretics, has been precipitated by *Rautrax* therapy to date.

Minor gastro-intestinal disturbances and muscle cramps have been noted. Although investigators have observed a few cases of pruritus, neither skin eruptions nor allergic reactions have been reported.

There are no absolute contra-indications to the use of *Rautrax*. Hypochloræmic alkalosis may occur with or without hypokalemia. Patients on *Rautrax* therapy should, therefore, be examined regularly for fluid and/or electrolyte imbalance.

**Supply.** *Rautrax* is supplied as capsule-shaped tablets containing 400 mg. flumethiazide; 50 mg. whole root *Rauwolfia serpentina* (Raudixin) and 400 mg. potassium chloride.

Bottles of 25.

**Dosage.** 2 to 6 tablets daily in divided doses initially (2 to 4 usually sufficient); adjustable within range of 1 to 6 tablets (1 or 2 usually sufficient).

**Note.** In patients already on ganglionic blocking agents, veratrum and/or hydralazine, reduce the dosage of such agents by at least 50% when adding *Rautrax*.

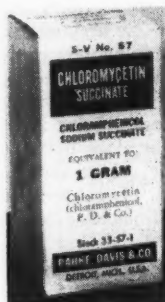
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## CHLOROMYCETIN SUCCINATE

A NEW 'THREE-WAY' PARENTERAL FORM OF  
CHLOROMYCETIN

Parke, Davis Laboratories (Pty.) Ltd., have introduced *Chloromycetin Succinate*, a readily available and exceptionally well tolerated form of broad-spectrum antibiotic therapy suitable for administration by any of the three parenteral routes—intravenous, intramuscular and subcutaneous. *Chloromycetin Succinate* can also be given by inhalation in certain respiratory conditions.

**Description:** *Chloromycetin Succinate* is the sodium salt of the monosuccinic ester of Chloromycetin. It is highly soluble in water and parenteral fluids and so is easily prepared for use. It produces minimal tissue reaction at the injection site. Once injected, the ester is rapidly hydrolysed by tissue enzymes, giving effective therapeutic concentrations of free and active Chloromycetin within the body.



**Indications:** *Chloromycetin Succinate* is active against the usual wide range of Chloromycetin-sensitive infections. The fact that adequate therapeutic blood levels can be maintained with almost complete absence of local tissue reactions makes *Chloromycetin Succinate* particularly well-suited to paediatric use.

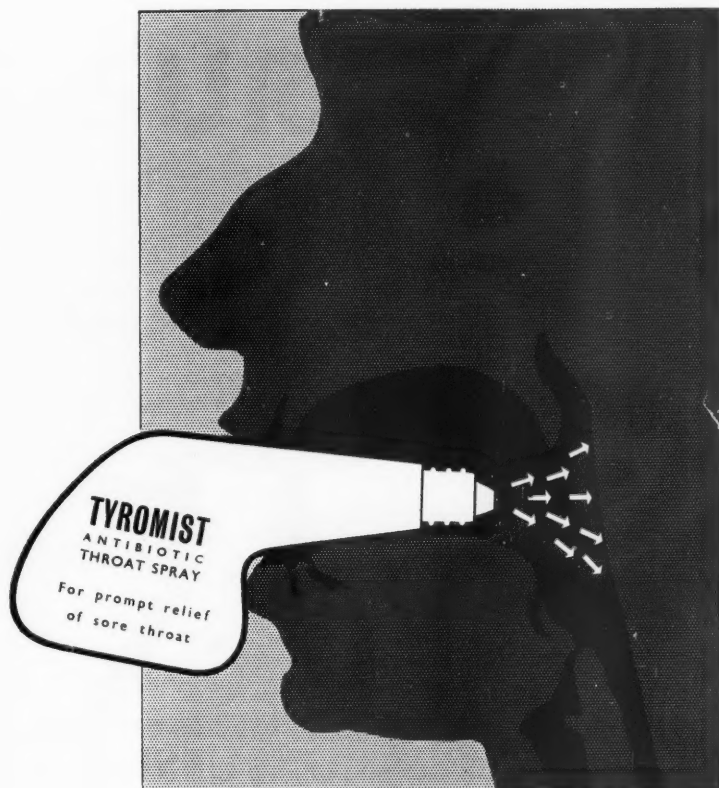
*Chloromycetin Succinate* also lends itself well to the treatment of patients with enteric disease in its acute phase, when nausea, vomiting or severe diarrhoea might interfere with the effective absorption of oral medication.

An excellent agent for the treatment of various meningitides, including *H. influenzae* meningitis, *Chloromycetin Succinate* has been reported highly effective in the treatment of a number of respiratory infections, including acute tracheobronchitis, asthmatic bronchitis, bronchial and pneumococcal pneumonia. In the last mentioned indications it is of particular interest to know that the high solubility and rapid hydrolysis of *Chloromycetin* makes possible its use as an aerosol spray in the relief of chronic or subacute respiratory illness with bacterial infection.

**Dosage and Administration:** The gelsiccated powder in the *Steri-Vial* is prepared for injection by the addition of an aqueous diluent such as Water for Injection or 5% Dextrose Injection. Full instructions for the preparation of a solution accompany each vial, together with recommended dosage schedules for the various age groups.

**Package Information:** *Chloromycetin Succinate* is supplied in 10 c.c. *Steri-Vials*, each containing the equivalent of 1 gm. of Chloromycetin.

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### Chapter

- I Introductory
- II The Nature of the Prostitute and of Prostitution
- III The Prostitute and Her Collaborators
- IV The Prostitute and Her Clients
- V The Prostitutes Themselves
- VI The Prostitutes Themselves (continued)
- VII Prostitution and its Evils
- VIII Prostitutes and their Families
- IX The Prostitute and the Community
- X Social Control
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- XII Social Control (continued)
- XIII General Conclusions · Recommendations · The Prospect

*Appendices:* Questionnaires · Schema of Venereological Examination Employed · Schema of Sexological Examination Employed · Glossary · References · Index

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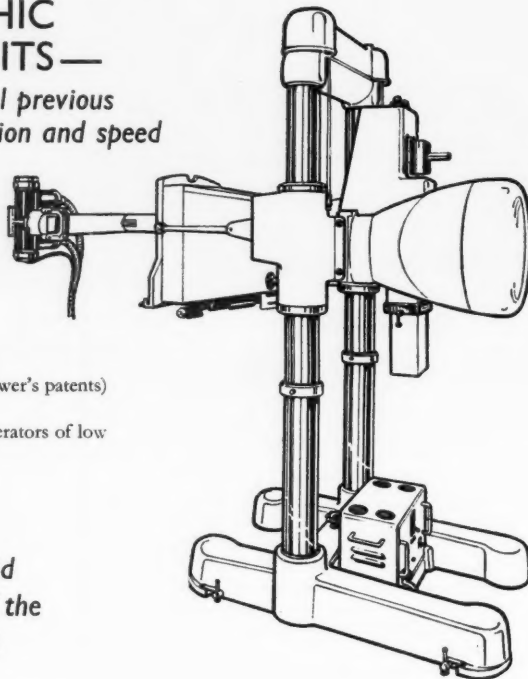
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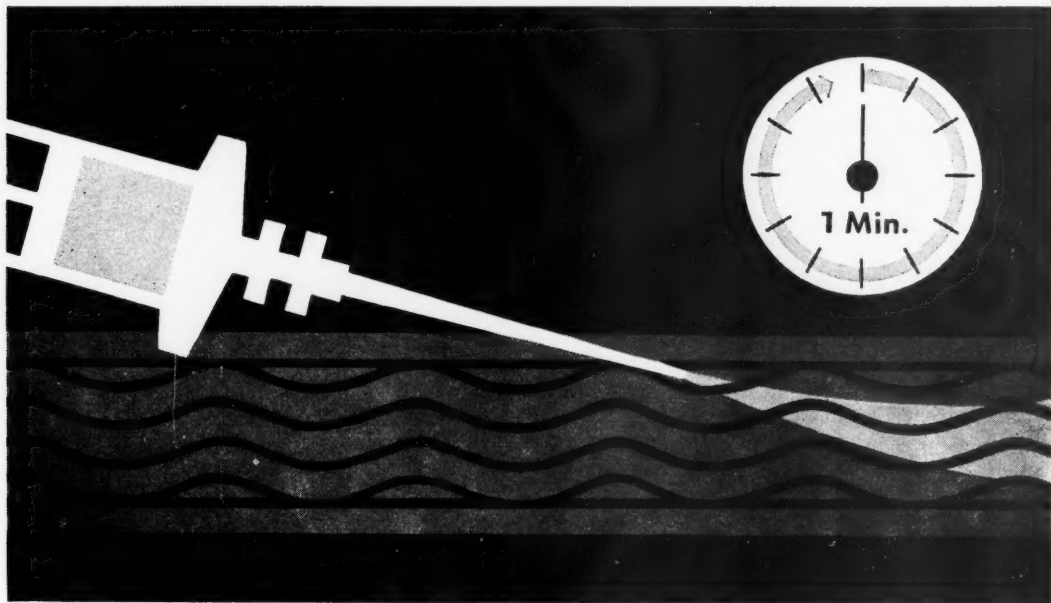
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